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Title: METHOD OF TREATING ALOPECIA ;
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AU651354, AU8081991, CA2082505, CS9101945, DE69109115D, DE69109115T, EP0536182 (WO9200057), B1, ES2074276T, HU212051, HU9500598, IE65868, IE912207, IL98608, JP3007146B2, PT98089, SK278895, ZA9104889

ABSTRACT:

Method of treating individuals with alopecia or having inferior quality hair, by administering to the scalp of said individuals an effective amount of ketoconazole. Novel compositions comprising as an active ingredient ketoconazole and an inert carrier.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP91/01136 (22) International Filing Date: 19 June 1991 (19.06.91) (30) Priority data: 9014221.7 26 June 1990 (26.06.90) GB (71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventor; and (75) Inventor/Applicant (for US only) : PIERARD, Gérald, E. [BE/BE]; Rue du Sart-Tilman 402, B-4031 Angleur (BE). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: METHOD OF TREATING ALOPECIA (57) Abstract Method of treating individuals with alopecia or having inferior quality hair, by administering to the scalp of said individuals an effective amount of ketoconazole. Novel compositions comprising as an active ingredient ketoconazole and an inert carrier.		

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Method of treating alopecia

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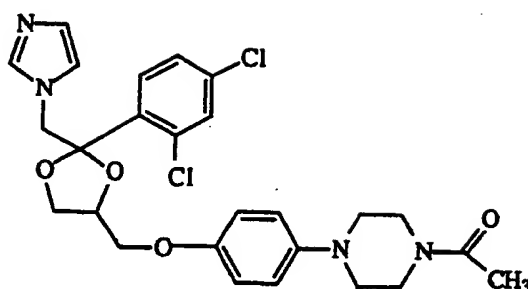
A healthy, thick and uniform hair growth on the scalp is generally considered an important aesthetic aspect of the human body. The loss of hair or any imperfection in the quality of the hair is consequently often experienced a very undesirable feature of one's physical appearance.

The fact that a majority of the male population is genetically predisposed to lose progressively its hair and the knowledge that current modes of treatment are very few, with a low number of individuals effectively responding to the treatment, more than amply illustrate the scope and magnitude of the problems involved and the need for additional therapies effective in reversing, arresting or retarding loss of hair and improving the quality of hair.

It has now been found that ketoconazole can effectively reverse, arrest or retard the loss of hair as experienced in alopecia and further, that ketoconazole does have a beneficial effect on the quality of hair.

The present invention is concerned with a method of treating individuals suffering from alopecia, said method comprising administering to said individuals the compound ketoconazole or a pharmaceutically acceptable acid addition salt thereof, in an amount effective in reversing, arresting or retarding said alopecia. Further, the present invention also is concerned with a method of treating individuals having an inferior quality of hair, said method comprising administering to said individuals the compound ketoconazole or a pharmaceutically acceptable acid addition salt thereof, in an amount effective in ameliorating the quality of hair.

Ketoconazole as mentioned hereinabove is the generic name of the compound (\pm)-cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine, which may be represented by the formula



The compound ketoconazole used in the method of the present invention is a known antifungal agent and its preparation as well as its pharmacological properties are described in US-4,335,125.

The compound ketoconazole can be used as such or in a pharmaceutically acceptable acid addition salt form, the latter being conveniently obtained by treating the base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

The term acid addition salt form as used hereinabove also comprises the solvates which the compound ketoconazole and its acid addition salts are able to form. Examples of such solvates are e.g. the hydrates, alcoholates and the like.

The term alopecia as used herein is meant to comprise the loss of hair from the scalp but also from the beard in humans. More in particular, the term alopecia relates to androgenetic alopecia or male pattern alopecia (baldness) which is characterized by the progressive, diffuse, symmetrical loss of hair from the scalp, typically starts at the frontal end of the scalp and gradually spreads to the vertex, ultimately leaving only a sparse peripheral band of hair covering the temples and occiput.

Since alopecia is a condition which at present can hardly be treated at all, the present finding that ketoconazole may effectively be employed in treating individuals suffering from alopecia, more in particular individuals with early androgenetic alopecia, is surprising. In this regard the term effectively means that treatment with ketoconazole results in the reversal, the arrest or the retardation of loss of hair and in the improvement of the quality of hair, in particular of the thickness of hair as can be gauged by

measuring the calibre of the hairs. The term early androgenetic alopecia means male pattern baldness classified as type I, II, III, IV or V on the Hamilton scale.

The term quality of hair as used herein relates to desirable physical properties of hair such as strength, thickness, density, uniformity and sensibility of hair. Inferior strength may manifest itself, for example, by splitting or by breaking. The thickness of a hair most commonly is expressed by its diameter or calibre. Density is meant to define the number of hairs per unit area, whereas uniformity relates to the constancy or gradual change of said density in contiguous areas of the scalp. Sensibility of hair refers to the presence of tactile sense in hair.

The compound ketoconazole and its acid addition salts used in the methods of the present invention are most preferably applied to the affected areas of the scalp or beard in the form of appropriate compositions, in particular compositions usually employed for the topical administration of drugs or cosmetic compositions. Said compositions contain the active ingredient ketoconazole, preferably in a 0.1 to 5% concentration (weight by volume), and any known dermatologically acceptable carrier and may take a wide variety of forms such as, for example, liquid forms, e.g. solutions, or suspensions in aqueous or oily mediums; or semi-liquid formulations, e.g. creams, hydrogels, gels, pastes, ointments, salves, tinctures and the like.

Other such compositions are preparations of the cosmetic type, such as toilet waters, packs, lotions, skin milks or milky lotions and shampoos. Said preparations contain, besides the active ingredient ketoconazole, components usually employed in such preparations. Examples of such components are oils, fats, waxes, surfactants, humectants, penetration enhancing agents, thickening agents, lipid absorbents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, perfumes, dyestuffs, lower alkanols, and the like. If desired, further active ingredients may be incorporated in the compositions, e.g. antiinflammatory agents, antibacterials, antifungals, disinfectants, vitamins, sunscreens, antibiotics or anti-dandruff agents. Interesting compositions for use in the methods according to the present invention are lotions and shampoos, typically containing from 0.2 to 2.5%, in particular 2% ketoconazole.

The lotions mentioned hereinabove are novel and have been especially developed for use in the methods of the present invention. Typically such lotions comprise 0.2 to 2.5%, in particular about 2% (w/v) of the active ingredient ketoconazole; propylene carbonate in an amount of from 20 to 40%, in particular from 20 to 30%, more in

particular about 25% (w/v); ethanol in an amount of from 25 to 55% in particular from 25 to 35%, more in particular about 28% (w/v); optionally any other components as defined hereinabove and usually employed in similar compositions; the remainder of the lotion being water.

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Particular instances of the aforementioned preparations are those which comprise a cyclodextrin or a derivative thereof. Said cyclodextrin or derivative thereof defines the topically acceptable unsubstituted and substituted cyclodextrins known in the art, in particular α -, β - or γ -cyclodextrins and the derivatives thereof, such as ethers, polyethers, mixed ethers.

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To prepare said cyclodextrin based formulations, ketoconazole is added to a solution of the cyclodextrin in water, preferably under vigorous stirring, and then adding the remainder of the ingredients. In the final compositions the amount of cyclodextrin is about 2 to 40%, in particular about 2.5 to 25%, more in particular about 5 to 20%.

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Other particular compositions for use in the methods of the present invention are those wherein the active ingredient ketoconazole is formulated in liposome-containing compositions. Different types of liposomes may be employed such as coarse (multilayer) liposomes or unilamellar liposomes and the like, which are formed, for example, with phosphatidyl cholines, ethanolamines, serines, sphingomyelins, cardiolipins, plasmalogens, phosphatidic acids, cerebiosides and the like. The viscosity of the liposomes can be increased by addition of one or more thickening agents such as xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and mixtures thereof. The aqueous component may consist of water optionally in admixture with electrolytes, buffers and other ingredients such as preservatives. Preferred electrolytes are calcium, sodium and potassium chloride. The organic component may consist of a solvent such as ethanol, glycerol, propylene glycol, a polyethylene glycol and a suitable phospholipid such as, lecithin, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, lysophosphatidyl choline, phosphatidyl glycerol and the like. Other lipophilic additives which may be added to selectively modify the characteristics of the liposomes are, e.g. stearylamine, phosphatidic acid, tocopherol, cholesterol, lanolin and the like.

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For preparing ointments, creams, toilet waters, skin milks, and the like, typically from 0.1 to 10% in particular from 0.1 to 5% and more in particular from 0.2 to 2.5% of the active ingredient ketoconazole optionally in an acid addition form, is combined in intimate admixture with a skin-and-hair acceptable carrier. For the ease of preparing

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high-quality compositions finely divided particles, preferably micronized particles of the active ingredient ketoconazole and optionally of other solid components, are employed. In ointments or creams, the carrier for example consists of 1 to 20%, in particular 5 to 15% of a humectant, 0.1 to 10% in particular from 0.5 to 5% of a thickener and water; or said carrier may consist of 70 to 99%, in particular 20 to 95% of a surfactant, and 0 to 20%, in particular 2.5 to 15% of a fat; or 80 to 99.9% in particular 90 to 99% of a thickener; or 5 to 15% of a surfactant, 2-15% of a humectant, 0 to 80% of an oil, very small (<2%) amounts of preservative, colouring agent and/or perfume, and water. In a toilet water, the carrier for example consists of 2 to 10% of a lower alcohol, 0.1 to 10% or in particular 0.5 to 1% of a surfactant, 1 to 20%, in particular 3 to 7% of a humectant, 0 to 5% of a buffer, water and small amounts (<2%) of preservative, dyestuff and/or perfume. In a skin milk, the carrier typically consists of 10-50% of oil, 1 to 10% of surfactant, 50-80% of water and 0 to 3% of preservative and/or perfume. Other active ingredients may be incorporated at doses ranging from 0.005% to 0.5%, particularly from 0.01% to 0.1%. In the aforementioned preparations, all % symbols refer to weight by weight percentage. The humectant, surfactant, oil, other active ingredient, etc... referred to in said preparations may be any such component used in the pharmaceutical or cosmetic arts. Further, when in the above compositions one or more of the components make up the major part of the composition, the other ingredients can evidently be not present at their indicated maximum concentration and therefore will make up the remainder of the composition.

In many of the foregoing compositions it is advantageous to use micronized forms of ketoconazole, i.e. material having an average particle size of less than 10 microns since the high surface area will facilitate the dissolution.

The liquid formulations mentioned hereinbefore may be packaged advantageously in any dosage dispensing device adapted for topical administration. In particular the present formulations, and especially the novel lotions described hereinabove may be applied as aerosols, e.g. by using an inert compressed gas as a propellant such as nitrogen or carbon dioxide, or alternatively by using a pump spray.

A preferred device for use according to the present invention comprises an atomizer or sprayer comprising a lotion as defined hereinabove and carbon dioxide as a propellant.

In still a further aspect of the present invention there is provided the use of the compound ketoconazole as defined above, for the manufacture of a medicament for reversing, arresting or retarding alopecia, or for improving the quality of hair.

- The ketoconazole containing compositions are applied topically to the area to be treated at regular intervals, as needed or convenient, e.g. at each washing occasion or thereafter. The duration of the treatment will depend upon the nature, extent and severity of the condition to be treated, as well as the frequency of application of the composition. No special precautions are needed other than those typical precautions which normally apply when administering drugs to the skin or hair.

Examples

10 A. Composition examples

Example 1 : Ketoconazole 2% cream

	ketoconazole	20 mg
	propylene glycol	200 mg
15	stearyl alcohol	75 mg
	cetyl alcohol	20 mg
	sorbitan monostearate	20 mg
	polysorbate 60	15 mg
	isopropyl myristate	10 mg
20	sodium sulfite anhydrous	2 mg
	polysorbate 80	1 mg
	purified water	q.s. ad 1g

- Stearyl alcohol, cetyl alcohol, sorbitan monostearate and isopropyl myristate are introduced into a doublewall jacketed vessel and heated until the mixture has completely molten. This mixture is added to a separately prepared mixture of purified water, propylene glycol and polysorbate 60 having a temperature of 70 to 75°C while using a homogenizer for liquids. The resulting emulsion is allowed to cool to below 25°C while continuously mixing. A solution of ketoconazole, polysorbate 80 and purified water and a solution of sodium sulfite anhydrous in purified water are next added to the emulsion while continuously mixing. The cream is homogenized and filled into suitable tubes.

Example 2 : 2% topical gel

35	ketoconazole	20 mg
	hydroxypropyl β -cyclodextrine	200 mg
	propylene glycol	50 mg
	ethyl alcohol 95% (v/v)	50 mg

carrageenan PJ	10 mg
hydrochloric acid	q.s. until solution
sodium hydroxide	q.s. ad pH 6.0
purified water	q.s. ad 1 g.

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Method of Preparation

To a solution of hydroxypropyl β -cyclodextrine in purified water is added ketoconazole while stirring. Hydrochloric acid is added until complete solution and then sodium hydroxide is added until pH 6.0. This solution is added to a dispersion of carrageenan PJ in propylene glycol while mixing. While mixing slowly the mixture is heated to 50°C and allowed to cool to about 35°C whereupon the ethyl alcohol is added. The rest of the purified water is added and the mixture is mixed until homogeneous.

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Example 3 : 2% topical cream

15	ketoconazole	20 mg
	hydroxypropyl β -cyclodextrine	200 mg
	mineral oil	100 mg
	stearyl alcohol	20 mg
	cetyl alcohol	20 mg
20	glycerol monostearate	20 mg
	glycerol	50 mg
	sorbate 60	15 mg
	polysorbate 60	35 mg
	hydrochloric acid	q.s. until solution
25	sodium hydroxide	q.s. ad pH 6.0
	purified water	q.s. ad 1 g.

Method of Preparation

To a solution of hydroxypropyl β -cyclodextrine in purified water is added ketoconazole while stirring. Hydrochloric acid is added until complete solution and next sodium hydroxide is added until pH 6.0. While stirring, glycerol and polysorbate 60 are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of mineral oil, stearyl alcohol, cetyl alcohol, stearyl monostearate and sorbate 60 having a temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest of the purified water is added and the mixture is mixed until homogeneous.

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Example 4 : 2% liposome formulation

	ketoconazole microfine	2 g
	phosphatidyl choline	20 g
	cholesterol	5 g
5	ethyl alcohol	10 g
	methyl paraben	0.2 g
	propyl paraben	0.02 g
	disodium edetate	0.15 g
	sodium chloride	0.3 g
10	hydroxypropylmethylcellulose	1.5 g
	purified water	ad 100 g

Method of Preparation

A mixture of ketoconazole microfine, phosphatidyl choline, cholesterol and ethyl alcohol is stirred and heated at 55-60°C until complete solution and is added to a solution of methyl paraben, propyl paraben, disodium edetate and sodium chloride in purified water while homogenizing. Hydroxypropylmethylcellulose in purified water is added and the mixing is continued until swelling is complete.

20 Example 5 : 2% liposome formulation

	ketoconazole microfine	2 g
	phosphatidyl choline	10 g
	cholesterol	1 g
	ethyl alcohol	7.5 g
25	hydroxypropylmethylcellulose	1.5 g
	sodium hydroxide (1 N)	ad pH 5.0
	purified water	ad 100 g

Method of Preparation

30 A mixture of phosphatidyl choline and cholesterol in ethyl alcohol is stirred and heated at 40°C until complete solution. Ketoconazole microfine is dissolved in purified water by mixing while heating at 40°C. The alcoholic solution is added slowly to the aqueous solution while homogenizing during 10 minutes. Hydroxypropylmethylcellulose in purified water is added while mixing until swelling is complete. The resulting solution
35 is adjusted to pH 5.0 with sodium hydroxide 1 N and diluted with the rest of the purified water.

Example 6 : 2% scalp lotion

	ketoconazole microfine	20 mg
	propylene carbonate	241.4 mg
	ethyl alcohol	282.8 mg
5	purified water	q.s. ad 1 ml

Method of Preparation

Ketoconazole microfine is stirred in a mixture of propylene carbonate and ethanol until completely dissolved. The resulting solution is diluted with purified water to the
10 required concentration. The resulting solution is filled in appropriate bottles or in
sprayers.

B. Clinical exampleExample 7

15 The utility of ketoconazole for treating alopecia can be demonstrated in the following test
procedure. 27 Men (22-31 years) having androgenetic alopecia Hamilton Grade II used
Nizoral® shampoo containing 2% ketoconazole during 60 weeks as often as
shampooing was considered necessary by each individual. The frequency of
shampooing varied between from 2 to 4 times weekly. Every 12 weeks trichograms
20 were recorded on the hair of the areas on the periphery of the alopecia. A hair index or
pilary index I_p was calculated by determining the proportion of hairs (A) (in %) in the
anagen phase of the hair cycle and multiplying by the mean diameter (C) (in μm) :
 $I_p = A \times C$. For adult individuals without androgenetic alopecia the I_p value is higher
than 60. In the 27 volunteers the mean I_p value was 18 at the beginning of this test and
25 did change little during the first 24 weeks of treatment. A significant increase in the I_p
value according to the U-test ($p < 0.05$) appeared at the 36th week. A net amelioration
of the pilary index was observed in the course of the treatment reaching approximately
twice its initial value after 60 weeks of treatment. These results indicate that
ketoconazole does have a beneficial effect in alopecia and improving the overall quality
30 of hair.

Claims


1. A method of treating individuals suffering from alopecia, said method comprising administering to said individuals the compound ketoconazole or a pharmaceutically acceptable acid addition salt thereof, in an amount effective in reversing, arresting or retarding said alopecia.
2. A method of treating individuals having an inferior quality of hair, said method comprising administering to said individuals the compound ketoconazole or a pharmaceutically acceptable acid addition salt thereof, in an amount effective in ameliorating the quality of hair.
3. The use of ketoconazole or a pharmaceutically acceptable acid addition salt thereof for the manufacture of a medicament for reversing, arresting or retarding alopecia.
4. The use of ketoconazole or a pharmaceutically acceptable acid addition salt thereof for the manufacture of a medicament for ameliorating the quality of hair.
5. A lotion comprising a dermatologically acceptable liquid carrier and as an active ingredient ketoconazole in an amount effective in reversing, arresting or retarding alopecia or effective in ameliorating the quality of hair.
6. A lotion according to claim 5 comprising from 0.1% to 5% (weight by volume) ketoconazole.
7. A lotion according to claim 6 comprising
 - from 0.2% to 2.5% of ketoconazole,
 - from 20% to 40% of propylene carbonate,
 - from 25% to 55% of ethyl alcohol,
 - the remainder of the lotion being water.
8. A process of preparing a lotion as defined in any of claims 5, 6 or 7 for reversing, arresting or retarding alopecia or effective in ameliorating the quality of hair, comprising intimately mixing ketoconazole with a dermatologically acceptable liquid carrier.
9. A sprayer comprising a composition as defined in any of claims 5 to 7.

10. A commercial package containing as an active ingredient ketoconazole together with instructions for the use thereof for reversing, arresting or retarding alopecia or for ameliorating the quality of hair.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 91/01136

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 7/06 A 61 K 31/495		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	British Journal of Dermatology, vol. 116, no. 2, February 1987 (GB), M.M. Carr et al.: "Treatment of seborrhoeic dermatitis with ketoconazole: I. Response of seborrhoeic dermatitis of the scalp to topical ketoconazole", pages 213-216, see page 213, line 1 - page 214, line 5; page 215, sub "Results" - page 216, paragraph 5 ---	4,5,6,8 ,9,10
X	British Journal of Dermatology, vol. 116, no. 2, February 1987, (GB), C.A. Green et al.: "Treatment of seborrhoeic dermatitis with ketoconazole: II. Response of seborrhoeic dermatitis of the face, scalp and trunk to topical ketoconazole", pages 217-221, see page 217 "Summary"; page 218, lines 3-9; page 220, sub "Discussion" - page 221, paragraph 2 --- -/-	4,5,6,8 ,9,10
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
19-09-1991	07 NOV 1991	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	 MISS T. TAZELAAR	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,4569935 (E.W. ROSENBERG et al.), 11 February 1986, see claims; column 1, line 67 - column 2, line 35; examples III, IV ---	4,5,6,8 -10
P,A	EP,A,0396184 (JANSSEN PHARMACEUTICA) 7 November 1990, see claims; examples 4,5 -----	5,6

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 1, 2, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT-Rule 39.1(iv): methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9101136
SA 48349

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 21/10/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4569935	11-02-86	US-A- 4491588	01-01-85
		US-A- 4942162	17-07-90
EP-A- 0396184	07-11-90	AU-A- 5471190	15-11-90
		JP-A- 2295927	06-12-90

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82